The role of substituents in retro Diels-Alder extrusion of CO_2 from 2(H)-pyrone cycloadducts

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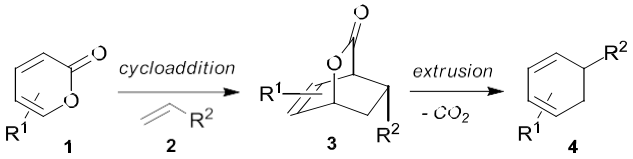
Abstract

An experimental and computational investigation is conducted into the role of substituents in retro Diels-Alder extrusion of CO_2 from 2-oxa-bicyclo[2.2.2]oct-5-en-3-ones. We provide the first experimental evidence that loss of CO_2 from the cycloadducts significantly depends on the nature and position of the substituents. For example, we show that whilst 5-carboethoxy-2-pyrone undergoes a more facile cycloaddition that 3-carboethoxy-2-pyrone, the cycloadduct from the latter pyrone undergoes a more facile loss of CO_2 than the cycloadduct from the former pyrone.

Keywords: Extrusion of CO2; Diels-Alder cycloaddition; 2(H)-pyrone; DFT; Synthesis; Role of substituents

1. Introduction

Diels-Alder cycloaddition of (2H)-pyran-2-ones, **1** with alkenes, **2**, followed by extrusion of CO_2 from the resulting bicyclic lactone **3**, is an excellent method for accessing synthetically valuable dihydrobenzenes, **4** (Scheme 1).[1] Often, these dihydrobenzenes can undergo *in situ* elimination, or oxidation, to afford substituted benzenes.[2] However, careful control of reaction conditions allows these functionally rich six membered rings to be isolated and used in the synthesis of natural products and medicinally useful compounds. For example, this combined cycloaddition-extrusion methodology is used by Posner in the synthesis of an analogue of vitamin D ,[3] by us in the synthesis of pseudodisaccharide libraries[4] and by others in the synthesis of reserpine,[5] α-yohimbine[5] and related berbanes,[6] a morphine fragment,[7] copane and ylangane skeleton,[8] gibberellic acid and zizaenes skeletons;[9] dihydroisoindolinone and isoquinolone,[10] 2-arylthio-2-cyclohexenone,[11] and medicinally useful barrelanes.[12]



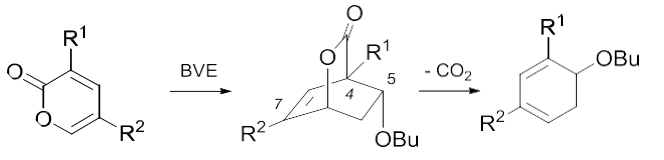
Scheme 1. The formation of bicyclic lactone **3** from 2(H)-pyran-2-one **1** and extrusion of CO_2 from **3** to afford dihydrobenzene **4**

Although the methodology has proven useful, as the above examples show, a more widespread use is hampered by a lack of understanding of the role of substituents in facilitating the extrusion reaction. In fact, whilst Posner[13,14a] and we[14b,15] have demonstrated how substituents can facilitate the cycloadditions of (2H)-pyran-2-ones, little is known about the role of substituents in the extrusion step. Interestingly, a number of recent publications hint at a significant role for substituents. For instance, the *in situ* cycloaddition/CO_2 extrusion methodology is highly facile for the synthesis of benzoates starting from either a 3- or 5-carbomethoxy substituted (2H)-pyran-2-one.[2,17] However, whilst a similar strategy for the preparation of bromobenzenes from 3-bromo-(2H)-pyran-2-one is also successful (albeit under harsher conditions), one using 5-bromo-(2H)-pyran2-one is not.[18] Since (2H)-pyran2-ones substituted with both carbomethoxy[19,15d] and bromo[14,16] groups undergo the cycloaddition step easily, these two observations may highlight a difference in the role of the substituents, not only in the cycloaddition step, but also in the extrusion step.

In view of our track record in this area,[4,15] we set out to initiate an experimental and computational study of the role of substituents on facilitating the extrusion of CO_2 from 2-oxa-bicyclo[2.2.2]oct-5-en-3-ones e.g. **3**. For the investigation reported here, we decided to compare two substituents, carboxylate and bromide, at two positions of the cycloadduct, 4- and 7-, given the same substituent (OBu) at position 5- (Scheme 2). We chose these particular systems not only because they map onto existing examples,[17,18] but also because based on literature precedence,[3,21] we expected a facile loss of CO_2 from the bicyclic lactone. Therefore, we can investigate not only the influence of the substituents on the extrusion reaction itself, but also compare it with that of the initial cycloaddition step directly.

2. Results and Discussion

We set out to compare the extrusion of CO_2 from bicyclic lactones **5**-**8**. The chosen examples enable us to investigate both the role of the substituents (CO_2R *vs* Br in comparing **5** and **7**) and their position (3-CO_2Me *vs* 5-CO_2Et in comparing **5** and **6**). Bicyclic lactones **5**-**8** were prepared by heating the corresponding 2(H)-pyran-2-ones **9**-**12** in a large excess of butyl vinyl ether (BVE) in a sealed tube. The isolated and purified cycloadducts **5**-**8** were then heated in dichloromethane in a sealed tube to affect the loss of CO_2 (Scheme 2). The sealed tubes can be immersed in an oil bath allowing careful control of temperature. The NMR analysis of the reaction mixtures showed that both **5** and **6** undergo clean and smooth loss of CO_2 to exclusively afford the corresponding cyclohexadienes **13** and **14** over a range of temperatures (45-150 °C). We could also detect a slow extrusion reaction when heating **7** at this temperature range, but none when heating **8**.



9 $R^1 = CO_2Me$, $R^2 = H$ | **5** $R^1 = CO_2Me$, $R^2 = H$ | **13** $R^1 = CO_2Me$, $R^2 = H$
10 $R^1 = H$, $R^2 = CO_2Et$ | **6** $R^1 = H$, $R^2 = CO_2Et$ | **14** $R^1 = H$, $R^2 = CO_2Et$
11 $R^1 = Br$, $R^2 = H$ | **7** $R^1 = Br$, $R^2 = H$ | **15** $R^1 = Br$, $R^2 = H$
12 $R^1 = H$, $R^2 = Br$ | **8** $R^1 = H$, $R^2 = Br$

Scheme 2. Cycloadditions of 2(H)-pyran-2-ones with BVE and the extrusion of CO_2 from the cycloadducts

In addition, we experimentally determined energy barriers for these reactions. We measured the rates of cycloadditions to afford the bicyclic lactones, and the rates of extrusion of CO_2 from bicyclic lactones **5**-**7** (Scheme 2) over a range of temperatures (45-150 °C). Cycloadduct **8** did not afford any extrusion product at temperatures up to 150 °C and underwent extensive decomposition to unidentified compounds at higher temperatures. Therefore it was not possible to calculate a rate for its reaction.

Since the dienophile in the cycloaddition step (BVE) is used in large excess, the cycloaddition steps are effectively first order in the (2H)-pyran-2-ones, whilst the extrusion reactions are unimolecular and are also first order. Thus it was possible to determine rate constants in each reaction. Using these data, we determined the activation energy for the extrusion of CO_2 from the cycloadducts using an Arrhenius plot (see supporting information). The results are shown below (Table 1, computationally calculated energy barriers for the formation of **5**-**7** and **13**-**15** are also given, see later).

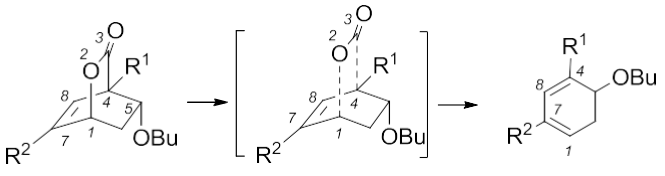
		Relative relationship between energy barriers in Kcal mol^{-1}	
		Experimental	Calculated[b]
Cycloaddition	**10→6**	0.0 (6.6)[a]	0.0 (17.4)
	9→5	2.1 (8.7)	1.7 (19.1)
	11→7	7.9 (14.5)	6.1 (23.5)
Loss of CO_2	**5→13**	0.0 (21.6)	0.0 (25.9)
	6→14	4.8 (26.4)	2.8 (28.7)
	7→15	N/A	3.2 (29.1)

[a] Absolute values in brackets [b] Sum of electronic and thermal energies at 298K.

Table 1. Experimental and computed values for the relative activation barrier to the cycloaddition and extrusion.

It is clear from these data, that both the position and the nature of substituents play a significant role in the extrusion process.

The extrusion of CO_2 from **5**, which has a carbomethoxy substituent at the 4 position, has a lower energy barrier and therefore is more facile than that for **6**, which has a carboethoxy at the 7 position. In addition, the energy barriers for the extrusion of CO_2 from **7** and **8**, which have a bromo substituent at the 4 and 7 positions respectively, are considerably higher than that for **5** or **6**, which have ester substituents at the corresponding positions. The higher energy barrier for **8** means that it can undergo other reaction pathways, seen as decomposition, instead of extrusion, when heated to higher temperatures



5, **6**, **7** **16**, **17**, **18** **13**, **14**, **15**

5, **13**, **16** $R^1 = CO_2Me$, $R^2 = H$; **6**, **14**, **17** $R^1 = H$, $R^2 = CO_2Et$;
7, **15**, **18** $R^1 = Br$, $R^2 = H$

Scheme 3. Extrusion of CO_2 from the cycloadducts.

Computational methods such as DFT are used by us[15a,20] and other groups,[22] to successfully rationalise the outcome of Diels-Alder cycloadditions, by calculating the geometry and relative energetics of the transition states. We argued that application of this method to the extrusion (retro Diels-Alder or rDA) reaction, should also enable the correct prediction of the relative energy barriers for the extrusion reactions. Therefore, we employed this computational method to estimate the energy barriers for the cycloadditions and extrusion steps (Table 1).

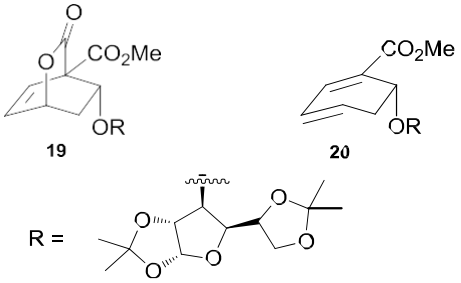


Figure 1. Structures of **19** and **20**.

The transition states for the loss of CO_2 from **5**, **6** and **7**, (structures **16**-**18**), are shown above (Scheme 3). The calculated bond lengths for **16**-**18** are also provided (Table 2). To have confidence that the computed geometries for the transition states are reliable we used the bond lengths reported for **19**[4b] (CCDC code HUNPUC) and **20**[4b] (CCDC code USOHIU) (Figure 1), as a close approximation for the starting lactones (**5**, **6** and **7**) and cyclohexadienes (**13** and **14**) respectively. It should be noted that compounds **19** and **20** are the only known examples with crystal structures of a cycloadduct/diene pair in extrusion reactions.

As can be seen (Figure 2), the extrusion reaction is asynchronous with a significantly more advanced C-O bond cleavage than the C-C bond cleavage in the transition state (TS), as suggested by White.[23] We note that asynchronicity in the TS **16**-**18** correlates with the energy barrier for the loss of CO_2 from their corresponding starting materials **5**-**7**. We had previously shown that the asynchronicity in bond formation in the transition states is a predictor of more facile reactions during Diels-Alder (DA) reaction.[15a] As a corollary to that, asynchronicity in bond cleavage in the transition states during retroDA appears to be a predictor of more facile extrusion reaction.

	Bond lengths (Å)				
	19[a]	**16**	**17**	**18**	[a]
C1-O2	1.47(1)	2.20(5)	2.11(5)	2.14(2)	
O2-C3	1.33(3)	1.24(3)	1.24(2)	1.24(3)	1.20[b]
C3-C4	1.52(5)	1.80(6)	1.86(6)	1.87(6)	
C4-C8	1.51(4)	1.42(1)	1.43(5)	1.42(8)	1.35(7)
C7-C8	1.32(6)	1.39(7)	1.38(2)	1.38(5)	1.48(9)
C1-C7	1.49(1)	1.39(5)	1.39(9)	1.39(5)	1.35(1)

[a] values from X-ray crystal structure. [b] C=O bond in CO_2

Table 2. Comparison between the computed bond lengths in transition states **16**, **17** and **18** and values from **19** and **20**.

In many examples in the literature, the extrusion of CO_2 occurs *in situ* following the cycloadditions of 2(H)-pyran-2-ones. In order to compare the role of substituents in the cycloaddition with extrusion steps, we also measured and calculated the energy barriers for the formation of **5**-**7** from the corresponding 2(H)-pyran-2-ones **9**-**11** (Table 1). Interestingly, conversion of **10** to **6** has a lower energy barrier than conversion of **9** to **5**, whereas conversion of **6** to **14** has a higher energy barrier than conversion of **5** to **13**. In other words, in a combined cycloaddition/extrusion reaction, factors that appear to facilitate the first (cycloaddition) step might retard the second (extrusion) step. This unexpected observation can lead to the identification of the rational choice of substituents in a diene and dienophile that can afford only the cycloadduct, without the extrusion. These findings may also explain the recent contrasting observations by Wagner and Harrity[18] about the reactivity of bromopyrones in combined cycloaddition-extrusion reactions.

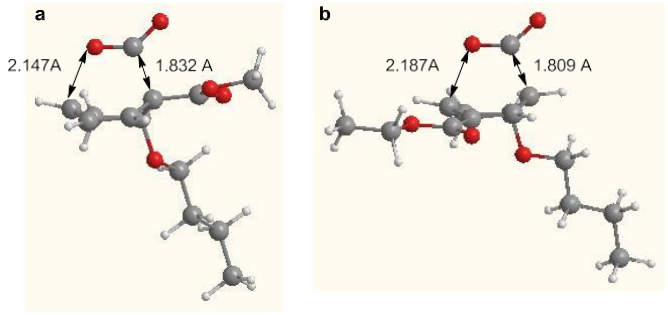


Figure 2. TS geometries for the conversion of **5** to **13** (a) & **6** to **14** (b).

Further experimental and computational work is required to enable a definitive explanation of these observations. At this stage however, we can speculate on a possible reason to explain why a carbomethoxy group at the C-4 position facilitates extrusion of CO_2. Presumably the electron withdrawing carbomethoxy group at the C-4 position stabilises any increasing electron charge on O-2, to which it is antiperiplanar. This in turn contributes to the asynchronicity in bond cleavage and stabilises the transition state for the loss of bridging CO_2.

3. Conclusions

In summary, we have provided a framework to investigate how substituents can influence the extrusion of CO_2 from 2-oxa-bicyclo[2.2.2]oct-5-en-3-ones which is highly useful for deciding on whether the two stage cycloaddition/extrusion reaction should be done stepwise or *in situ*. We have shown that extrusion from lactone cycloadducts with an electron withdrawing carboxy substituent at the 4-position is more facile than one with a

substituent at the 7-position. In contrast, cycloaddition of 5-carboxy substituted (2H)-pyran2-one which affords the 4-substituted cycloadducts are more facile than cycloaddition of 3-carboxy substituted (2H)-pyran2-one which affords the 7-substituted cycloadducts. Further investigations are currently underway in our group to expand these observations, with the aim of ascertaining the reasons for the role that specific substituents play in the extrusion reaction.

4. Experimental Section

Computational chemistry

All transition structures were initially optimized with AM1, then re-optimized using B3LYP/6-31G*. Frequency calculations showed that each transition structure had only one imaginary vibrational frequency, corresponding to the required reaction coordinate. All calculations were run with Gaussian 09, Revision A.02. All geometry optimizations were converged to within the default tolerances, and the default FineGrid used for all numerical integrations. The energies of butyl vinyl ether, structure **9** and structure **10** were determined independently and also as super-molecule calculations of **9** with BVE and **10** with BVE. In the super-molecule calculations the two molecules were placed at 10Å distance apart, to ensure that barrier heights were the same as when the structures were determined separately. Furthermore, the values obtained for the sum of electronic and thermal energies were not adversely affected by the presence of the six extra vibrational degrees of freedom present in the super-molecule calculations. Schematic diagrams showing total internal energy differences between critical points and tables listing energies of molecules and transition states for the Diels-Alder and the extrusion reactions are given in the supporting information.

Synthetic chemistry

Compunds **10**,[24] **11**[25] and **12**[25] were prepared according to previously published procedures. All other starting material were commercially available. Characterisation of compounds **7**,[15a] **8**,[15a] **19**[4b] and **20**[4b] are previously reported.

5-*endo*-Butoxy-3-oxo-2-oxa-bicyclo[2.2.2]oct-8-ene-4-carboxylic acid methyl ester **5** A solution of 3-carbomethoxy-2(H)-pyran-2-one **9** (537 mg, 3.48 mmol) and butylvinyl ether (5 mL) was heated for 44 h at 60 ^{o}C in a sealed tube. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (pre-washed with petrol/EtOAc/Et_3N (92:6:2), eluting with petroleum ether/EtOAc (5:1) to give the title compound **5** (680 mg, 77%) as a pale yellow oil.; IR: (thin film) 2957, 2925, 2868, 1755, 1739, 1438, 1351, 1280, 1095, 975 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.84 (t, 3H, *J* = 7.6 H-4'), 1.24 (sextet, 2H, *J* = 7.6 Hz, H-3'), 1.37-1.45 (m, 2H, H-2'), 1.65 (dt, 1H, *J* = 1.7, 13.8 Hz, H-6), 2.56 (ddd, 1H, *J* = 3.8, 7.6, 13.8 Hz, H-6), 3.29-3.33 (m, H, H-1'), 3.42-3.46 (m, H, H-1'), 3.88 (s, 3H, OCH_3), 4.33 (dt, 1H, *J* = 7.6, 1.2 Hz, H-5), 5.23 (ddd, 1H, *J* = 1.7, 3.6, 6.9 Hz, H-1), 6.56 (dd, 1H, *J* = 5.2, 7.7 Hz, H-7), 6.76 (dd, 1H, *J* = 0.9, 7.7 Hz, H-8); ^{13}C NMR ($CDCl_3$, 150.9 MHz): δ 13.76 (C-4'), 19.16 (C-3'), 31.62 (C-2'), 35.28 (C-6), 52.94 (OCH_3), 61.48 (C-4), 69.98 (C-1'), 72.79 (C-5), 74.30 (C-1), 129.75 (C-8), 130.57 (C-7), 167.68 (C=O), 168.84 (C=O); LRMS (ESI$^+$): 272.2 $[M+NH_4]^+$; HRMS (ESI) calcd for $C_{13}H_{22}O_5N$ $[M+NH_4]^+$: 272.1492; Found: 286.1490.

5-*endo*-Butoxy-3-oxo-2-oxa-bicyclo[2.2.2]oct-8-ene-7-carboxylic acid ethyl ester **6**, A solution of ethyl coumalate **10** (581 mg, 2.37 mmol) and butylvinyl ether (4 mL) was heated for 24 h at 100 ^{o}C in sealed tube. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (pre-washed with petrol/EtOAc/Et_3N (92:6:12)), eluting with petroleum ether/EtOAc (2:1) to give the title compound **6** (486 mg, 76%) as a yellow oil. IR: (thin film) 2960, 1762, 1713, 1465, 1381, 1334, 1297, 1255, 1160, 1096, 1027, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H, *J* = 7.4 H-4'), 1.26-1.32 (m, 5H, H-3', OCH_2CH_3), 1.47 (q, 2H, *J* = 6.9 Hz, H-2'), 1.58 (dt, 1H, *J* = 14.3, 1.6 Hz, H-6), 2.60 (ddd, 1H, *J* = 3.8, 7.7, 14.3 Hz, H-6), 3.33-3.37 (m, H, H-1'), 3.43-3.46 (m, H, H-1'), 4.04-4.05 (m, 1H, H-5), 4.09 (dd, 1H, *J* = 3.6, 6.2 Hz, H-5), 4.23-4.26 (m, 3H, OCH_2CH_3), 5.67 (ddd, 1H, *J* = 1.9, 3.8, 7.4 Hz, H-1), 7.19 (d, 1H, *J* = 6.0 Hz, H-8); ^{13}C NMR ($CDCl_3$): δ 13.76 (C-4'), 14.25 (OCH_2CH_3), 19.29 (C-3'), 31.65 (C-2'), 34.95 (C-6), 47.64 (C-4), 61.37 (OCH_2CH_3), 69.33 (C-1'), 71.48 (C-5), 73.45 (C-1), 136.14 (C-8), 138.07 (C-7), 162.23 (C=O), 170.83 (C=O); LRMS (ESI$^+$): 286.2 $[M+NH_4]^+$; HRMS (ESI) calcd for $C_{14}H_{24}O_5N$ $[M+NH_4]^+$: 286.1649; Found: 286.1656.

Methyl 6-butoxycyclohexa-1,3-dienecarboxylate **13**, A solution of compound **5** (208 mg, 0.818 mmol) and DCM (2 mL) was heated for 36 h at 100 ^{o}C in sealed tube. The reaction mixture was cooled to room temperature and evaporated at reduced pressure. The crude product was purified by flash chromatography on silica gel, eluting with petroleum ether/EtOAc (5:1) to give title compound **13** (163 mg, 95%) as a pale yellow oil. Spectroscopic data in agreement with those previously published. ^{1}H NMR ($CDCl_3$): δ 0.84 (t, 3H, *J* = 7.56 H-4'), 1.30 (sextet, 2H, *J* = 7.39 Hz, H-3'), 1.37-1.49 (q, 2H, J = 6.87 Hz, H-2'), 2.37-2.47 (m 1H, H-5), 2.80 (ddd, 1H, *J* = 1.20, 5.50, 19.42 Hz, H-5), 3.29-3.33 (dt, H, J = 6.70, 9.28 Hz, H-1'), 3.50 (dt, H, J = 6.70, 9.28 Hz, H-1'), 3.78 (s, 3H, OCH_3), 4.37 (d 1H, *J* = 6.87 Hz, H-6), 6.17-6.23 (m, 1H, H-3, H-4), 7.23 (d, 1H, *J* = 5.33 Hz, H-2); ^{13}C NMR ($CDCl_3$): δ 13.95 (C-4'), 19.36 (C-3'), 30.34 (C-2'), 32.15 (C-5), 51.78 (OCH_3), 67.08 (C-6), 68.32 (C-1'), 122.86 (C-3), 126.22 (C-1), 133.15 (C-4), 135.46 (C-2), 167.76 (C=O); LR-MS (ES$^+$): 228.2 $[M+NH_4]^+$.

Ethyl 4-butoxycyclohexa-1,5-dienecarboxylate **14** A solution of compound **6** (1.24g, 4.62 mmol) and DCM (2 mL) was heated for 16 h at 138 ^{o}C in a sealed tube. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel, eluting with petroleum ether/EtOAc (10:1) to give *title compound* **14** (158 mg, 15 %) as a pale yellow oil and starting material (893 mg). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, 3H, *J* = 7.4 H-4'), 1.29 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 1.34 (q, 2H, *J* = 7.4 Hz, H-3'), 1.51 (q, 2H, *J* = 6.7 Hz, H-2'), 2.56 (ddd, 1H, *J* = 3.8, 8.3, 19.4 Hz, H-3), 2.66 (dt, 1H, *J* = 19.4, 5.3 Hz, H-3), 3.41 (t, 1H, *J* = 6.7 Hz, H-1'), 3.42 (t, 1H, *J* = 6.7 Hz, H-1'), 4.05 (dddd, 1H, *J* = 0.9, 4.5, 6.7, 8.3 H-4), 4.1 (q, 3H, *J* = 7.2 Hz, OCH_2CH_3), 6.0 (dd, 1H, *J* = 4.3, 10.0 Hz, H-5), 6.62 (dt, 1H, *J* = 0.9, 10.0 Hz, H-6), 7.01 (dddd, 1H, *J* = 0.9, 2.4, 3.8, 5.3 Hz, H-2); ^{13}C NMR ($CDCl_3$): δ 14.02 (C-4'), 14.38 (OCH_2CH_3), 19.46 (C-3'), 30.15 (C-3), 32.25 (C-2'), 60.68 (OCH_2CH_3), 67.56 (C-1'), 69.32 (C-4), 123.95 (C-6), 126.25 (C-5), 127.82 (C-1), 136.33 (C-2), 165.47 (C=O); LRMS (ESI$^+$): $[M+NH_4]^+$; HRMS (ESI) calcd for $C_{13}H_{24}O_3N$ $[M-H]^+$: 223.1334; Found: 223.1329.

Acknowledgments

We thank EPSRC (MHA), Yorkshire Cancer Research (KA) and Yorkshire Enterprise Fellowships (KA) for financial support. Computations were carried out using the Imperial College London High Performance Computing service.

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Supplementary Material

Details and results of experimental and computational methods. Copies of ^{1}H and ^{13}C NMR spectra for compounds **13** and **14**.